US EPA ARCHIVE DOCUMENT

Dr. Schmidt

ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

001147

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Sencor - Request for a temporary tolerance residues for (4-amino-6-(1,1-dimethylethyl)-3-(methylthio)-1,2,4-triazin-5(4H)-one and its triazinone metabolites in or on potatoes at 0.3 ppm.

Mr. Lee E. TerBush, Acting Chief
Coordination Branch
Registration Division

Pesticide Petition No. 3G1368

Chemagro Chemical Co.
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Kansas City, Missouri 64120

Dr. G. E. Whitmore reviewed the original petition (0G0940) on 3/10/70 for Sencor and found a subacute no-effect level of 150 ppm in the rat and dog. This no-effect level supported a tolerance of 0.02 ppm on potatoes and soybeans.

On 8/17/72 Dr. W. E. Parkin reviewed petition 2F1274 and found that the data submitted would only support negligible residue tolerances and recommended for a temporary tolerance of 0.1 ppm in soybeans. He further recommended that "if the petitioner desires a non-negligible tolerance, carcinogenicity studies, a reproduction study, and a teratology study would also be necessary".

In a response t (PP# 2F1274) on 11/3/72, Dr. Parkin responded to Mr. W. S. Cox regarding an unidentified residue totaling 0.5 ppm in soybeans. However, he stated that these compounds are not susceptible to hydrolysis by enzymes or to acid hydrolysis at room temperature. Because of this stability, TB did not find these compounds to be toxicologically significant. TB therefore concluded that only the negligible tolerance of 0.1 ppm could be safely supported.

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A review of the data submitted with petition 3G1368 follows:

2 year chronic feeding studies in dogs and rats.

A. 6 Month Interim Report 3502 - Bayer AG, Institut für Toxikologie

Four to 6 month old beagle dogs were individually housed and fed levels of 0, 25, 100 and 1500 ppm, each dose group contained 4 males and 4 females. Clinical-Laboratory examinations were made at the start and again at 2, 4, and 6 months. These tests are as follows:

Blood tests - Hgb, Sed. rate, RBC, WBC, Hct, Differential blood count, prothrombin time, MCV,

Liver Function tests - ALP, SGOT, SGPT, OCT, bilirubin, Protein and BSP.

Urine and Kidney tests - Sugar, blood, bile, protein and microscopic

Post-mortems - all dogs that died were examined macroscopically for pathological changes.

Results

All parameters in the blood tests were normal at the 25 and 100 levels. However, at the 1500 ppm level there was increased sedimentation, decreased Hct, decreased WBC, increased RBC, and the number of Lymphocytes were reduced in favour of the proportion of mature polymorphonuclear neutrophils.

All parameters at all dose levels in the liver function tests were within normal limits.

Urine examinations, kidney function tests, blood sugar and cholesterol levels were reported to be within the normal limits at all levels.

Three animals died at the 1500 ppm level, 2 males and 1 female. All three were reported to have died with severe foamy pneumonia. Both males were reported to exhibit severe emaciation but other organs were reported to show no symptoms. The mucous membranes of the intestine of the female were reported to be red and some parts of the intestine contained chyme mixed with blood. We estimate that 100 ppm is the no-effect dose level. DOG NOEL = 100 ppm

B. 6 Month Interim Report 35051 - Bayer AG, Institut für Toxikologie

Forty-five male and 45 female Wistar rats per group were fed levels 0, 25, 35, 100 and 300 ppm. Similar examinations were made to those in the dog study reported previously.

Results

Food consumption and body weights were compared with the controls. None of the levels fed have shown any adverse effects on any of the parameters tested. These results show that in the rat the no-effect level is 300 ppm. RAT, NOEL = 300 ppm

3-Generation Reproduction Study - Bayer AG, Institut für Toxikologie

Fb 30 strain of Elberfeld breed rats are being used for this study. Thirty five-day old rats were divided into 4 groups and fed at the following levels 0, 35, 100 and 300 ppm. The standard procedure for producing the F/1a and b, F/2a and b and the F/3a and b is being followed. Two female rats were housed with 1 male for 19 or 20 days and each female was never housed with 3 different males for longer than 1 cycle. After the matings the females were individually housed.

Immediately after gestation the pups were weighed and numbers recorded. The number of offspring was reduced to 10 per litter and they were nursed for up to 4 weeks during which time they were weighed weekly. At the end of 4 weeks the offspring from the first mating were sacrificed and examined for malformation. The second mating is to be maintained for further matings.

Results to date indicate that there is no significant reproduction difference between the 100 ppm level and the controls. In the group which received the 300 ppm level the fertility index bordered on the norm for this strain of rats. Future progress reports are forthcoming.

18 Month Carcinogenicity Study (34481) - Industrial BIO-TEST Laboratories

Swiss white mice were fed Sencor at levels of 1,250 and 2,500 ppm for 18 months. Three positive control groups, 2 fed N-nitroso diethylamine at dietary levels of 10 and 40 ppm and 1 fed Benzidine at 1,000 ppm plus an untreated control group. The following table shows the distribution of mice fed:

Group	Test Material	Dietary Level (ppm)	Number of Animals Males	Females
Control	None	None	125	125
Positive Control-I	N-Nitroso diethylamine	10	125	125
Positive Control-II*	N-Nitroso diethylamine	40	60	60
Positive Control-III	Benzidine	1,000	0	100
Test-I	Sencor (Bay 94337)	1,250	125	125
Test-II	Sencor (Bay 94337)	2,500	125	125

* Positive Control-II group was sacrificed after six months of feeding.

Data obtained are as follows:

Hematologic Studies

Blood samples collected individually from ten mice of each sex from the control and both test groups after 18 months of feeding were analyzed for the following:

1. Hematocrit Value
2. Erythrocyte Count
3. Hemoglobin Concentration
4. Total Leukocyte Count
5. Differential Leukocyte Count

Clinical Blood Chemistry Studies

Blood samples collected individually from ten mice of each sex from the control and both test groups after 18 months of feeding were pooled in groups of five samples per group and were analyzed for the following:

1. Blood Urea Nitrogen (BUN) Concentration
2. Serum Alkaline Phosphatase (SAP) Activity
3. Serum Glutamic-Pyruvic Transaminase (SGPT) Activity
4. Fasted Blood Glucose Concentration

Pathologic Studies

Complete gross pathologic examinations for tumor formation were conducted upon all postmortem animals and all animals sacrificed in extremis. All tumors were submitted for histopathologic examination and classification.

Following six months of feeding, all of the Positive Control-II group mice were sacrificed by carbon dioxide asphyxiation and autopsied. After 18 months of feeding, all surviving mice were sacrificed and autopsied. At the time of gross examination a complete set of organs and other tissues was removed from each mouse and preserved in formalin solution.

Microscopic examination of tissues taken from ten mice of each sex from the Control, Positive Control-I, Test-I and Test-II groups, from 15 mice of each sex from the Positive Control-II and from 15 mice from the Positive Control-III groups was conducted. The following tissues, stained with Hematoxylin-Eosin, were included: esophagus, stomach (cardia, fundus and pylorus), small intestine (duodenum, jejunum and ileum), cecum, colon, liver, kidneys, spleen, pancreas, urinary bladder, adrenal gland, testes, seminal vesicle, ovary, bone marrow, thyroid gland, salivary gland, prostate gland, heart, aorta, lung, lymph node (cervical and mesenteric), skeletal muscle, peripheral nerve, bone (femur), spinal cord, uterus, trachea, eye, optic nerve and brain (cerebrum, cerebellum and pons).

Results

There was an increased number of mortalities in the animals fed Sencor but no signs of tumor formation either grossly or microscopically. However, there was focal to diffuse hyperplasia of hepatocytes in the livers of the Positive Control-I animals which was classified as minimal to mild in severity. Similar conditions were found in Positive Control-II which were classified as minimal to moderate in severity. Positive Control-III animals exhibited hepatomas, some animals from all three positive groups had alveolagenic carcinomas in the lungs. From these data it was concluded that Sencor was not carcinogenic.

Conclusions

At the proposed level of residue of 0.3 ppm on potatoes the average daily intake of Sencor from potatoes would be 0.027 mg. In the original petition reviewed by Dr. G. Whitmore the no-effect level based on a dog and rat study was found to be 150 ppm. However, in the current submitted data the petitioner has established a 100 ppm no-effect level in [redacted] dogs [redacted] from a 6 month interim report. If we assume the 2000 fold safety factor then a 60 kg man could safely tolerate from 0.075 to 0.15 mg/day which is well below the amount obtained from eating potatoes. In addition an 18 month mouse carcinogenicity study showed no effects for this parameter at 2,500 ppm.

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Recommendations

Chemistry Branch's considerations permitting, Toxicology Branch recommends that the temporary tolerance of 0.3 ppm residues for Sencor and its triazinone metabolites on potatoes be established. The safety of this material is supported by the data submitted with this and previous petitions.

Robert P. Schmidt 5/8/73

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Toxicology Branch
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cc: Chemistry Branch
Ecological Efffect Branch
Division Reading File
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